REMARKS

Claims 1- 36 were pending in the application. Claims 1-7, 12-15, 20-25, and 30-36 were withdrawn from consideration as being directed to a non-elected invention. Claims 8-11, 16-19 and 26-29 have been amended. Support for the amendments can be found in the specification at least at page 8, lines 25-28. Additional support for the amendments to claim 8 can be found in the specification at least at page 16, lines 9-11. Additional support for the amendments to claim 11 can be found in the specification at least at page 3, lines 28-29. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

The specification has been amended to correct for informalities, specifically reference to Figures 5A-5C and 12A-12F. Figure 11 has been amended to correct a minor typographical error. The foregoing amendment is not related to issues of patentability, and introduces no new matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

Rejection of Claims 8-11, 16-19, and 26-29 Under 35 U.S.C. § 112, Second Paragraph

I. Rejection of Claims 8, 16, 26 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 8, 16, and 26 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "active protein." The Examiner states that it is "unclear whether this is meant to distinguish a type and/or frequency of protein, the expression level, or the state of the protein's functionality." The Examiner has also rejected claims 8, 16, and 26 for use of the phrase "about" and states that the claims are indefinite "because the metes and bounds of the claimed range cannot be determined."

Applicants respectfully traverse the foregoing rejection on the grounds that claims 8, 16, and 26 particularly point out and distinctly claim the subject matter which Applicants regard as their invention, as required by 35 U.S.C. § 112, second paragraph. Applicants submit that based on the plain language of the claims and the teachings in Applicant's specification, claims 8, 16, and 26 are clear and definite to one of ordinary skill in the art.

Recitation of the term "active" is art-recognized and is intended to mean an Ig-fusion protein which is functional and binds with high affinity. Applicants distinguish the term "active" from "inactive" forms at page 9, lines 6-8 of the specification, as the form that binds with high affinity, whereas the "'inactive" form does not. In the specification, Applicants use the term "live" interchangeably with "active" and "dead" interchangeably with "inactive." Applicants explain at page 22, lines 22-26 of the specification that the term "dead form refers simply to a molecule that binds with a affinity (10-1000 fold) lower than the live form, i.e. it may not be [sic] completely lack binding activity, but instead has reduced affinity for ligand relative to the high affinity form found on cells naturally." Applicants also teach that active Ig-fusion proteins are folded correctly, as described at page 10, lines 28-29, versus misfolded or inactive proteins which are described at page 10, lines 8-9 of the specification. One of ordinary skill in the art knows that for a protein to function correctly it must be folded correctly. In view of the above, Applicants submit that the term "active" is clear and definite.

Recitation of the word "about" is art recognized and indicates any temperature within and around the specified range of 27°C to 32°C, as recited in claims 8 and 16, and the specified range of 10°C to 25°C in claim 26. Support for the term "about" can be found at page 10, lines 23-27 and at page 11, lines 2-4. In addition, Applicants provide working examples where ranges are given which include all of the intermediary temperatures within the claimed range. In Example 3 at page 16 of the specification, Applicants demonstrate that lowering the culture temperature to 28°C increases the yield of the active form of the Ig-fusion protein. Based on teachings from experiments described in Example 3 and shown in Figure 9, one of ordinary skill in the art would recognize that incubating mammalian cells at about 27°C and about 32°C would result in

improved yields of the active form of the protein. Applicants cannot be expected to test every temperature around 27°C, *i.e.* 26.5, 26.6., 26.7, 26.8, 26.9. Thus, Applicants use of the term "about" indicates temperatures immediately around 27°C, 32°C, 10° and 25°C, evidenced, for example, in Figure 8. Therefore, Applicants respectfully request that in view of the amendments to the claims and the reasons described above, the rejection under section 112 be reconsidered and withdrawn.

II. Rejection of Claim 16 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 16 under 35 U.S.C. § 112, second paragraph for using the term "the protein-Ig fusion" which the Examiner asserts is unclear. Applicants have amended claim 16 to recite the term "an Ig-fusion protein" in order to clarify that the Ig-fusion is a protein. Applicants clearly define the term "immunoglobulin fusion protein" in the specification at page 8, lines 25 to page 9, line 5. Applicants state at page 8, lines 25-28 that, " 'immunoglobulin fusion proteins' [we] refer to any fusion of any functional portions of the extracellular domain of a polypeptide with any portion of the immunoglobulin constant regions, e.g. the CH1, CH2, CH3 domains or combinations thereof." Applicants also teach that immunoglobulins can be fused to members of the TNF family of receptors. In view of the amendment and the clear and definite description of the term "Ig-fusion protein," Applicants respectfully request that the Examiner withdraw this 112 rejection.

III. Rejection of Claims 8-11, 16-19 and 26-29 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 8-11, 16-19, and 26-29 under 35 U.S.C. § 112, second paragraph for recitation of the word "fusion." The Examiner states that use of the term "fusion" is unclear because it does not describe what kind of fusion. Applicants have amended claims 8-11, 16-19, and 26-29 to specify that the fusion of the invention is an immunoglobulin-fusion protein. In view of this amendment, Applicants respectfully request that the Examiner withdraw the rejection.

IV. Rejection of Claims 10-11, 18-19 and 28-29 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 10-11, 18-19 and 28-29 under 35 U.S.C. § 112, second paragraph for use of the word "fragment." Applicant asserts that "fragment" is a term of art that would be recognized by one of ordinary skill in the art, and that the specification clearly supports use of the term. However, in view of the definition of the term Ig-fusion protein in the specification and in the interest of expediting prosecution, Applicants have amended the claims to delete reference to the term "fragment," rendering the rejection moot.

V. Rejection of Claims 11, 19, and 29 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 11, 19, and 29 under 35 U.S.C. § 112, second paragraph for using the abbreviation "HVEM". Applicants have amended the claims to recite the full description of the term, herpes virus entry mediator (HVEM). Thus, the rejection is rendered moot.

Accordingly, Applicants respectfully request that in view of the amendments to the claims and the reasons described above, the rejection under section 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 10, 11, 18, 19, 28, and 29 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 10, 11, 18, 19, 28, and 29 under 35 U.S.C. § 112, first paragraph. The Examiner states that fragments of the LT-β receptor are not described in the specification. Applicants respectfully traverse this rejection, however, in view of the definition of the term Ig-fusion protein in the specification and in the interest of expediting prosecution, Applicants have amended the claims to delete reference to the term "fragment," rendering the rejection moot.

In view of the above-mentioned amendments and arguments presented above, Applicant has addressed the 112 rejections with respect to claims 16-18 and 26-28. There are no 101 or prior art grounds f r rejecting these claims. Therefore, Applicants request that the Examiner indicate claims 16-18 and 26-28 as allowable and free of the prior art.

Rejection of Claims 11, 19, and 29 Under 35 U.S.C. §101

The Examiner has rejected claims 11, 19, and 29 under 35 U.S.C. §101 for specifically asserting a utility or a well established utility. The Examiner states that,

> The disclosed utilities for the HVEM protein include the treatment of immunological disease, including in vitro immune function. However, neither the specification nor any art of record teaches what the HVEM is, how it functions, or a specific and well-established utility claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. The asserted utility of the HVEM protein is based on the assertion that HVEM belongs to the TNF family.

Applicants respectfully traverse the foregoing rejection, and assert that a specific, substantial and well-established utility, which would have been credible to one skilled in the art at the time of the invention, is clearly disclosed in the instant specification.

Claim 11 is directed to an active Ig-fusion protein comprising HVEM, obtained by culturing a mammalian host cell transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C. Claim 19 is directed to a pharmaceutical preparation obtained by culturing a host transformed with DNA encoding an Ig-fusion protein comprising HVEM in a culture system having a low temperature of about 27° C to about 32 ° C, thereby expressing active Ig-fusion proteins, recovering active Ig-fusion proteins from the culture system, and combining the active Ig-fusion proteins with a pharmaceutically acceptable carrier. Claim 29 is directed to an active Ig-fusion protein comprising HVEM obtained by culturing yeast transformed with DNA encoding the fusion in a culture system having a low temperature of about 10° C to about 25 ° C.

HVEM is a member of the TNF receptor family, and is known to bind the ligand LIGHT. The chemical, physical, and biological properties of HVEM were well known in the art at the time of filing, as evidenced, for example, by reference CV, submitted in the Information Disclosure Statement (IDS) filed on January 9, 2002. Reference CV which published October 16, 1998, prior to the earliest priority date of the present application (*i.e.*, December 17, 1998),

describes the ligand to HVEM and includes functional descriptions of HVEM, including the ability of a HVEM-Fc fusion to block HVEM-ligand inhibition of adenocarcinoma cells (see page 27553, second column). In addition, Applicants teach that signaling performed by the TNF family of receptors "may have application in the treatment of immune based disease as well as the wide range of human diseases that have pathological sequelae due to immune system involvement" (see page 2, lines 18-21). Applicants also teach that soluble forms of a TNF family receptor can be used to modulate TNF-related signaling, and provide an example of such a modulation, namely a block of bone loss (see page 2, line 22 of the specification).

In addition, since the time of filing, HVEM has been linked with disorders commonly associated with members of the TNF receptor superfamily. For example, Applicants submit reference D3 in a supplemental IDS filed herewith. Reference D3 describes a role for TNFRSF14 (also called HVEM) in atherosclerosis based on expression and cell culture studies. In Figure 3 of reference D3, the authors demonstrate that TNFRSF14 can induce proinflammatory cytokines, including TNFα and IL-8.

As the Examiner is aware, Applicants do not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07. Based on the ample teachings in Applicant's specification regarding the role and importance of TNF family receptors, including HVEM, Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicant's asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101.

In view of all of the foregoing, Applicants assert that each of the utilities set forth in the specification for the invention as instantly claimed are specific, credible and substantial and/or well-established utilities that would have been recognized as such by one of skill in the art at the

time the application was filed. Therefore, the instant claims meet the requirements of 35 U.S.C. §101, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 8-10 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 8-10 as being anticipated by Crowe *et al.*(1994) *Science* 264:707 (hereinafter Crowe-Science) in view of Crowe *et al.*(1994) *J. Immunol. Methods* 168:79 (hereinafter Crowe-Immunol). The Examiner states that Crowe-Science teaches a fusion consisting of LT-β and a portion of an immunoglobulin, but does not "specifically disclose [of] temperature ranges." The Examiner relies upon Crowe-Immunol for "disclos[ing] culturing a host cell transformed with a DNA encoding the fusion at a temperature range of 27°C." Applicant respectfully traverses this rejection.

Claims 8 to 10 are directed to an active immunoglobulin fusion protein (Ig-fusion protein), including a member of the TNF family or a LT-B receptor obtained by culturing a mammalian host cell transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C.

As asserted by the Examiner, Crowe-Science does not teach or suggest culturing a mammalian host cell for expression of an immunoglobulin fusion protein at a low temperature. The Examiner relies on Crowe-Immunol as teaching culturing a host cell at a low range of 27° C. Applicants assert that Crowe-Immunol does not teach or suggest the claimed invention, namely culturing a transformed mammalian cell at about 27° C. As described on page 81, first column of Crowe-Immunol, the authors co-transfect a plasmid containing the p60:Fc-encoding cDNA (pVL1392-p60:Fc) or a plasmid containing the LTα cDNA (pVL1393- LTα) with a linearized polyhedrosis virus (AcNPV) to make recombinant baculovirus. The authors add this mixture to cells, incubate them at 27° C for 7 days, and amplify the resulting viral supernatants. Recombinant virus is then used to infect ***insect cells*** to produce the p60:Fc fusion. Crowe-Immunol does not describe culturing a mammalian host transformed with DNA encoding the fusion at a low temperature of about 27° C. Crowe-Immunol

teaches how to produce recombinant virus at a low temperature, but does not teach culturing host cells to express an immunoglobulin fusion protein.

As amended, claim 8 is directed to an active immunoglobulin fusion protein (Ig-fusion protein) obtained by culturing a ***mammalian host cell*** transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C. As Crowe-Science does not teach or suggest culturing an Ig-fusion protein obtained by culturing a ***mammalian host cell*** at a low temperature of about 27° C to about 35 ° C, Crowe-Science does not anticipate claim 8.

Dependent claims 9 and 10 are also not anticipated by Crowe-Science. Claim 9 is directed to an active immunoglobulin fusion protein (Ig-fusion protein) comprising a member of the TNF family obtained by culturing a ***mammalian host cell*** transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C. Claim 10 is directed to an active immunoglobulin fusion protein (Ig-fusion protein) comprising a LT-B receptor obtained by culturing a ***mammalian host cell*** transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C. Applicants assert that Crowe-Science does not anticipate dependent claims 9 and 10, because Crowe-Science does not anticipate claim 8 from which claims 9 and 10 depend.

Accordingly, Applicants respectfully request that the Examiner withdraw the §102 rejection of claims 8-10.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please amend the paragraph found at page 5, lines 16-19 of the specification as follows:

(Amended) **---Figure 5**: Ability of the flow through (lower) and eluted (upper) fractions from the AGH1 affinity column to bind to surface lymphotoxin (Figure 5A). Mean fluorescence intensity values were derived from a FACS analysis as described. Examples of the FACS profiles are shown on the right where the LTβR-Ig is compared to the binding of a control LFA-3-Ig protein (lower band, Figure 5B and upper band, Figure 5C).

Please amend the paragraph found at page 8, lines 7-12 of the specification as follows:

(Amended) --- **Figure 12**: A BIAcore analysis of the binding of either the LIGHT (Figures 12A-12C) or lymphotoxin-α (LTα) (Figures 12D-12F) ligands to BIA core chips immobilized HVEM-Ig generated at three different temperatures. Each curve shows a binding event at one concentration of ligand and the following concentrations were employed: 30, 15, 7.5, 1.87, 0.93, 0.47, 0.23, 0.11 and 0.0 μg/ml. Each chip was loaded to the same RU level indicating that equal amounts of receptor-Ig were bound.

Please amend Figure 11 as follows:

8/11

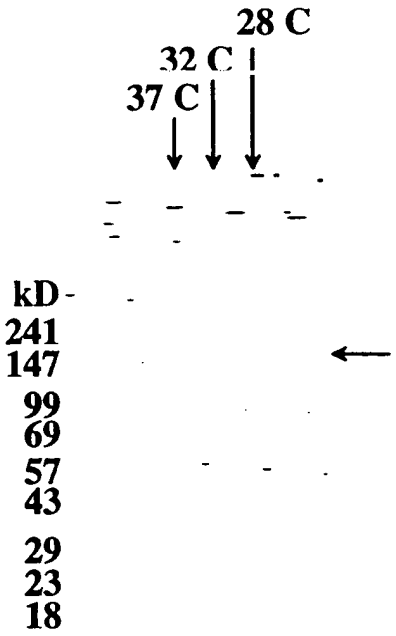
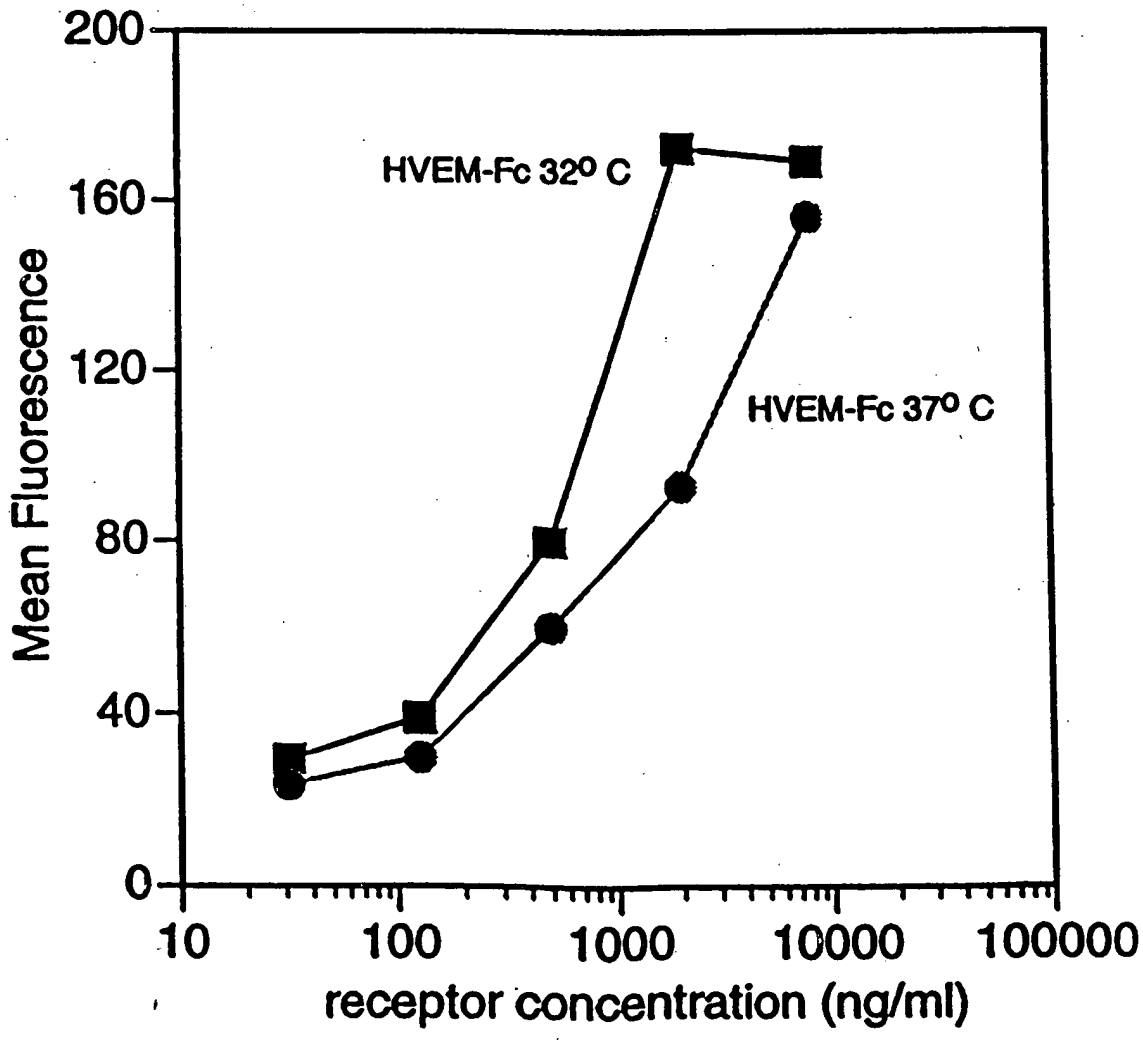


FIG. 10

FIG. 11A



In the claims:

8. **(Amended)** An active immunoglobulin fusion protein (Ig-fusion protein) ~~protein-Ig fusion~~ obtained by culturing a mammalian host cell transformed with DNA encoding the fusion in a culture system having a low temperature of about 27° C to about 35 ° C.

9. **(Amended)** The Ig-fusion protein of claim 8 comprising a member of the TNF family.

10. **(Amended)** The Ig-fusion protein of claim 9 comprising LT-B receptor, ~~or a fragment thereof~~.

11. **(Amended)** The Ig-fusion protein of claim 9 comprising herpes virus entry mediator (HVEM) ~~HVEM, or a fragment thereof~~.

16. **(Amended)** A pharmaceutical preparation obtained by

(d) culturing a host transformed with DNA encoding ~~the~~ an Ig-fusion protein ~~protein-Ig fusion~~ in a culture system having a low temperature of about 27° C to about 32 ° C, thereby expressing active an Ig-fusion proteins ~~protein-Ig fusions~~;

(e) recovering active an Ig-fusion proteins ~~protein-Ig fusions~~ from said culture system; and

(f) combining the active an Ig-fusion protein ~~protein-Ig fusions~~ of step (b) with a pharmaceutically acceptable carrier.

17. **(Amended)** The pharmaceutical preparation of claim 16 wherein the ~~protein-Ig fusion~~ Ig-fusion protein comprises a member of the TNF family.

18. **(Amended)** The pharmaceutical preparation of claim 17 wherein the ~~protein-Ig fusion~~ Ig-fusion protein comprises a lymphotoxin-B receptor ~~or a fragment thereof~~.

19. **(Amended)** The pharmaceutical preparation of claim 17 wherein the Ig-fusion protein ~~protein-Ig fusion~~ comprises HVEM, ~~or a fragment thereof~~.

26. **(Amended)** An active Ig-fusion protein ~~protein-Ig fusion~~ obtained by culturing yeast transformed with DNA encoding the fusion in a culture system having a low temperature of about 10° C to about 25 ° C.

27. **(Amended)** The Ig-fusion protein of claim 26 comprising a member of the TNF family.

28. **(Amended)** The Ig-fusion protein of claim 27 comprising LT-B receptor, or a fragment thereof.

29. **(Amended)** The Ig-fusion protein of claim 26 comprising HVEM, or a fragment thereof.

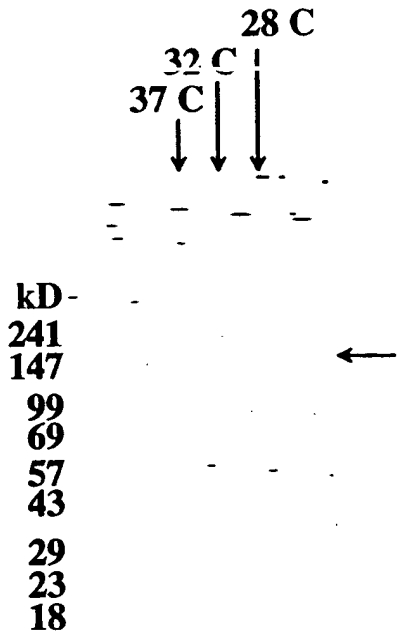


FIG. 10

FIG. 11A